Thyroid Hormones and Thermogenesis

ENDOCRINE BLOCK

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Objectives:

By the end of this lecture, the Second Year students will be able to:

- Describe the types and biosynthesis, actions and the regulation of thyroid hormones
- List and interpret the thyroid function tests
- Define goiter and differentiate between hypo- and hyperthyroidism
- Discuss the role of thyroid hormone in thermogenesis

Types and Biosynthesis of Thyroid Hormones

- Thyroxine (T_4) and tri-iodothyronine (T_3)
- Synthesized in the thyroid gland by:
  - Iodination and coupling of two tyrosine molecules
  - Binding to thyroglobulin protein
- Thyroid gland mostly secretes T_4
- Peripheral tissues (liver, kidney, etc.) de-iodinate T_4 to T_3
- Deiodination is catalyzed by deiodinase enzymes
- T_4 can be metabolized to rT_3 (inactive form)

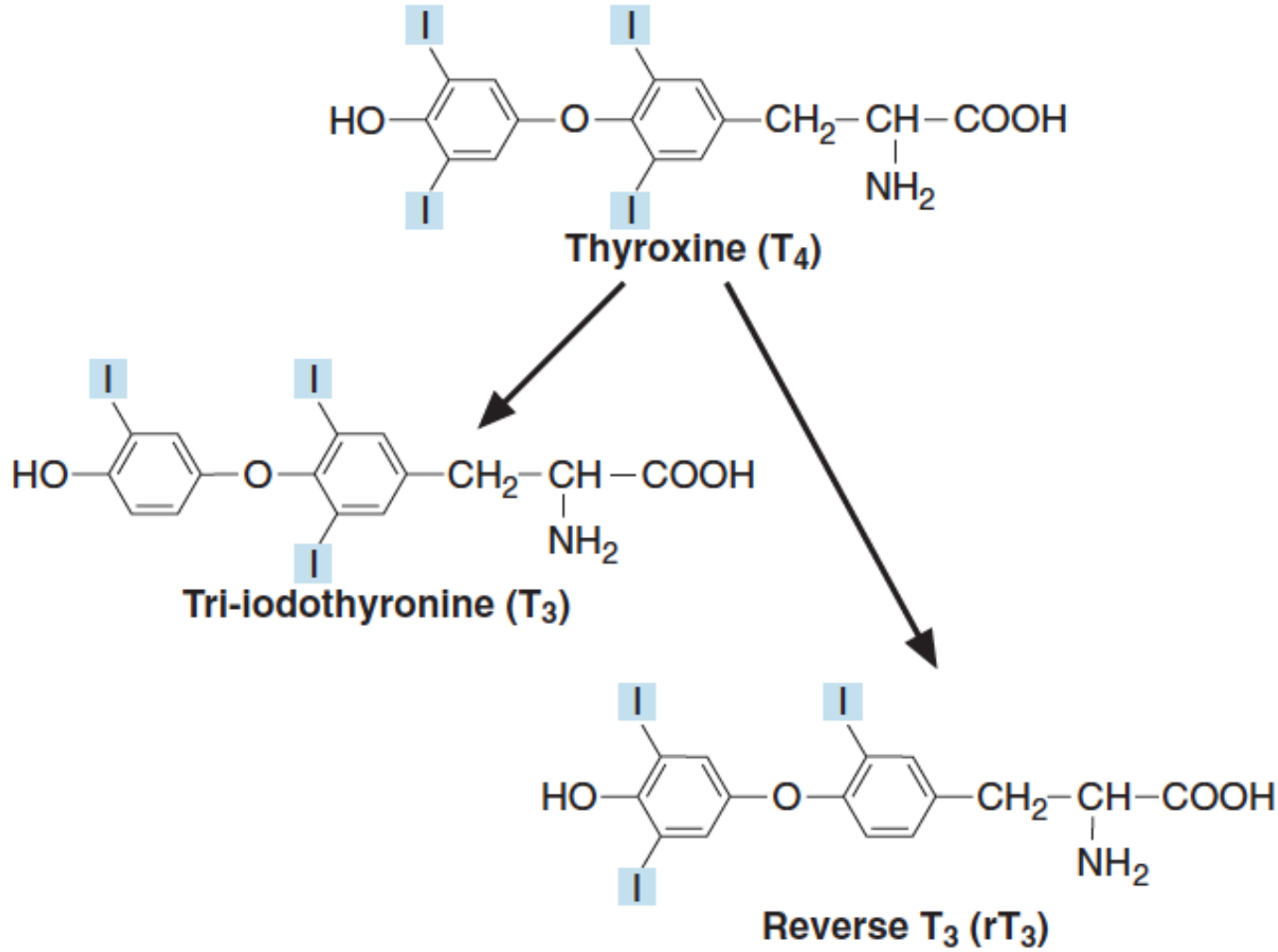


Fig 44.1 **The chemical structures of T_4, T_3 and rT_3.**

Types and Biosynthesis of Thyroid Hormones

- T_3 is more biologically active form
- Most of T_4 is transported in plasma as protein-bound
  - Thyroxin Binding globulin (TBG)-bound (70%)
  - Albumin-bound (25%)
  - Transthyretin (pre-albumin)-bound (5%)
- The unbound (free) form of T_4 and T_3 are biologically active

Thyroid hormone action

- Plays an essential role in maturation of all body tissues
- Involved in thermogenesis and metabolic regulation
- Increases cellular oxygen consumption and stimulates the metabolic rate
- Affects the rate of protein, carbohydrate and lipid metabolism

Thyroid Hormone Action

Clinical evidence of the wide spectrum of thyroid hormone action:

- Untreated congenital hypothyroidism →permanent brain damage
- Hypothyroid children have:
  - Delayed skeletal maturation →short stature
  - Delayed puberty
- Hypothyroid patients have high serum cholesterol due to:
  - Down regulation of LDL receptors on liver cells
  - Failure of sterol excretion via the gut

Regulation of Thyroid Hormone Secretion

- The hypothalamic-pituitary-thyroid axis regulates thyroid secretion

- The hypothalamus senses low levels of T_3/T_4 and releases thyrotropin releasing hormone (TRH)

- TRH stimulates the pituitary to produce thyroid stimulating hormone (TSH)

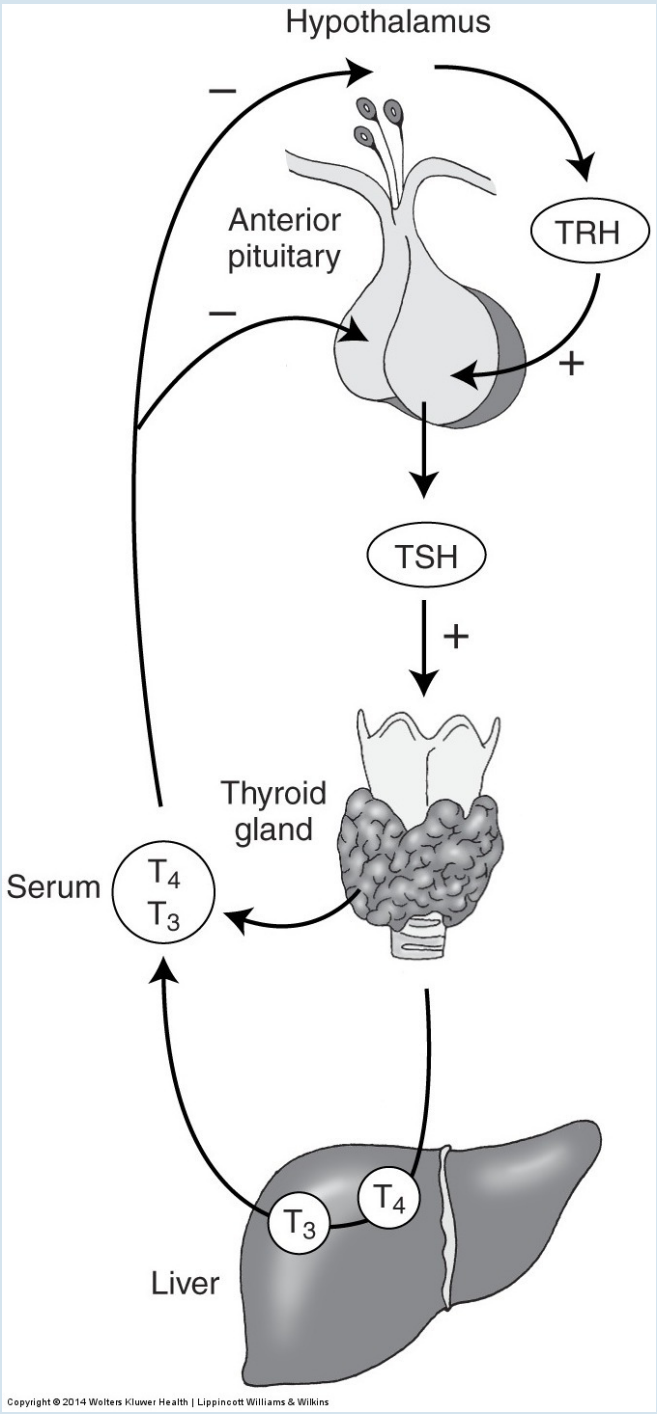
Regulation of Thyroid Hormone Secretion

- TSH stimulates the thyroid to produce T_3/T_4 until levels return to normal
- T_3/T_4 exert negative feed back control on the hypothalamus and pituitary
- Controlling the release of both TRH and TSH

Regulation of Thyroid Hormone Secretion

High thyroid hormone levels suppress TRH, TSH

Low thyroid hormone levels stimulate TRH, TSH to produce more hormone



Clinical Chemistry, Bishop, 7th Edition, pp. 492.

Thyroid Function Tests

I. **TSH measurement:**
   - Assessment of thyroid function
   - Highly sensitive test (detects very low conc.)

II. **Total T_4 or free T_4:**
   - Assessment of thyroid function
   - Monitors thyroid treatment (both anti-thyroid and thyroid replacement treatment)
   - TSH may take up to 8 weeks to adjust to new level during treatment

Thyroid Function Tests

III. **Total T_3 or free T_3:**
- Useful for assessing hyperthyroidism in which rise in T_3 is independent of T_4
- In some patients only T_3 rises (T_4 is normal): T_3 toxicosis
- For earlier identification of thyrotoxicosis

V. **Antibodies:**
- Diagnosis and monitoring of autoimmune thyroid disease:
  - Hashimoto's thyroiditis (antibodies against TSH receptors that suppress thyroid secretion
  - Graves' disease (antibodies against TSH receptors that stimulate thyroid secretion)

Goitre, Hypo and Hyperthyroidism

Enlarged thyroid gland

Goitre may be associated with:

- Hypofunction
- Hyperfunction
- Normal thyroid hormone conc. (euthyroid)

Causes:

- Iodine, selenium deficiency
- Hashimoto's thyroiditis
- Graves' disease (hyperthyroidism)
- Congenital hypothyroidism / thyroid cancer

Fig 44.2 **A patient with a goitre.**

Hypothyroidism

Deficiency of thyroid hormones

Primary hypothyroidism:

- Failure of thyroid gland (Elevated TSH, deficiency of thyroid hormones)

Secondary hypothyroidism:

- Failure of the pituitary gland to secrete TSH (rare)
- Failure of the hypothalamic-pituitary-thyroid axis

Hypothyroidism

- **Causes:**
  - Hashimoto's thyroiditis
  - Radioiodine or surgical treatment of hyperthyroidism
  - Drug effects
  - TSH deficiency
  - Congenital defects in thyroid synthesis / thyroid resistance
  - Severe iodine deficiency
- **Clinical features**
  - Tiredness / cold intolerance / weight gain / dry skin
- **Treatment**
  - Replacement therapy with levothyroxine (T4)

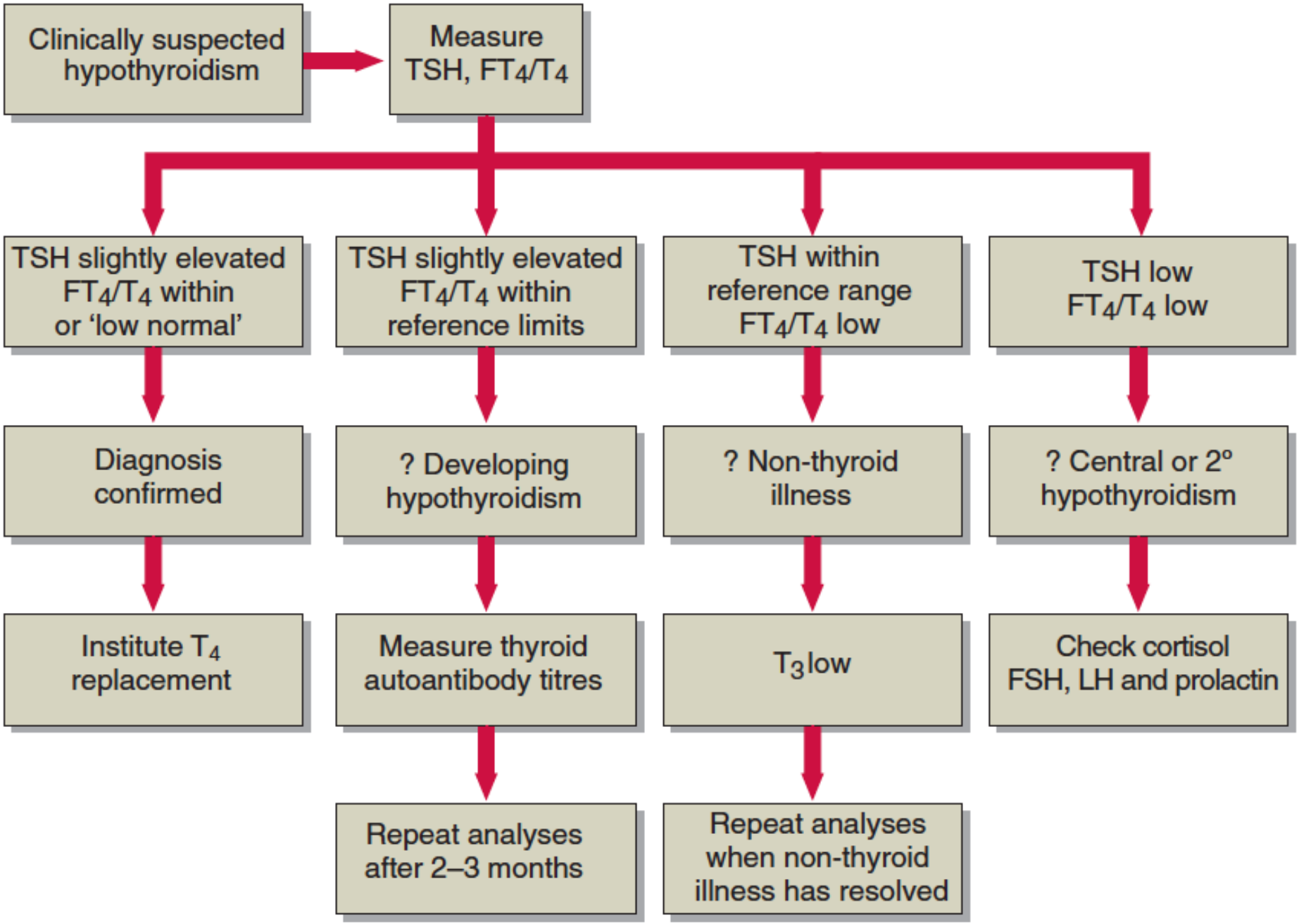


Fig 45.1 **Strategy for the biochemical investigation of suspected hypothyroidism.**

Hypothyroidism

Non-thyroidal illness

- In some diseases, the normal regulation of TSH, T_3 and T_4 secretion and metabolism is disturbed
- Most of T_4 is converted to rT_3 (inactive)
- Causing thyroid hormone deficiency
- Secretion of T_4 and T_3 is decreased

Hyperthyroidism

- Hyperstimulation of thyroid gland by pituitary gland
- Hypersecretion of thyroid hormones
- Tissues are exposed to high levels of thyroid hormones (thyrotoxicosis)

Causes:

- Graves' disease
- Toxic multinodular goitre
- Thyroid adenoma
- Thyroiditis
- Excessive intake of iodine / iodine drugs
- Excessive intake of T_4 and T_3

Hyperthyroidism

Clinical features:

- Weight loss with normal appetite
- Sweating / heat intolerance
- Fatigue
- Palpitation / agitation, tremor
- Angina, heart failure
- Diarrhea
- Eyelid retraction and lid lag

Fig 46.3 **Lid retraction and exophthalmos in a patient with Graves' disease.**

Graves' disease

- Most common cause of hyperthyroidism
- An autoimmune disease
- Due to antibodies against TSH receptors on thyroid gland
- The antibodies mimic the action of pituitary hormone
- Causing hypersecretion of thyroid hormone

Hyperthyroidism

Diagnosis

- Suppressed / undetectable TSH level
- Raised thyroid hormones levels
- Confirms primary hyperthyroidism

Problems in diagnosis

- Total serum T_4 varies due to changes in binding protein levels
- High estrogens in pregnancy increase TBG synthesis
- Total T_4 will be high, free T_4 will be normal

Hyperthyroidism

- Congenital TBG deficiency can also influence results
- Free T_4 and TSH are first-line tests for diagnosis of thyroid dysfunction

Treatment

- Antithyroid drugs: carbimazole, propylthiouracil
- Radioiodine: sodium ^{131}I inhibits T_4/T_3 synthesis
- Surgery: thyroidectomy

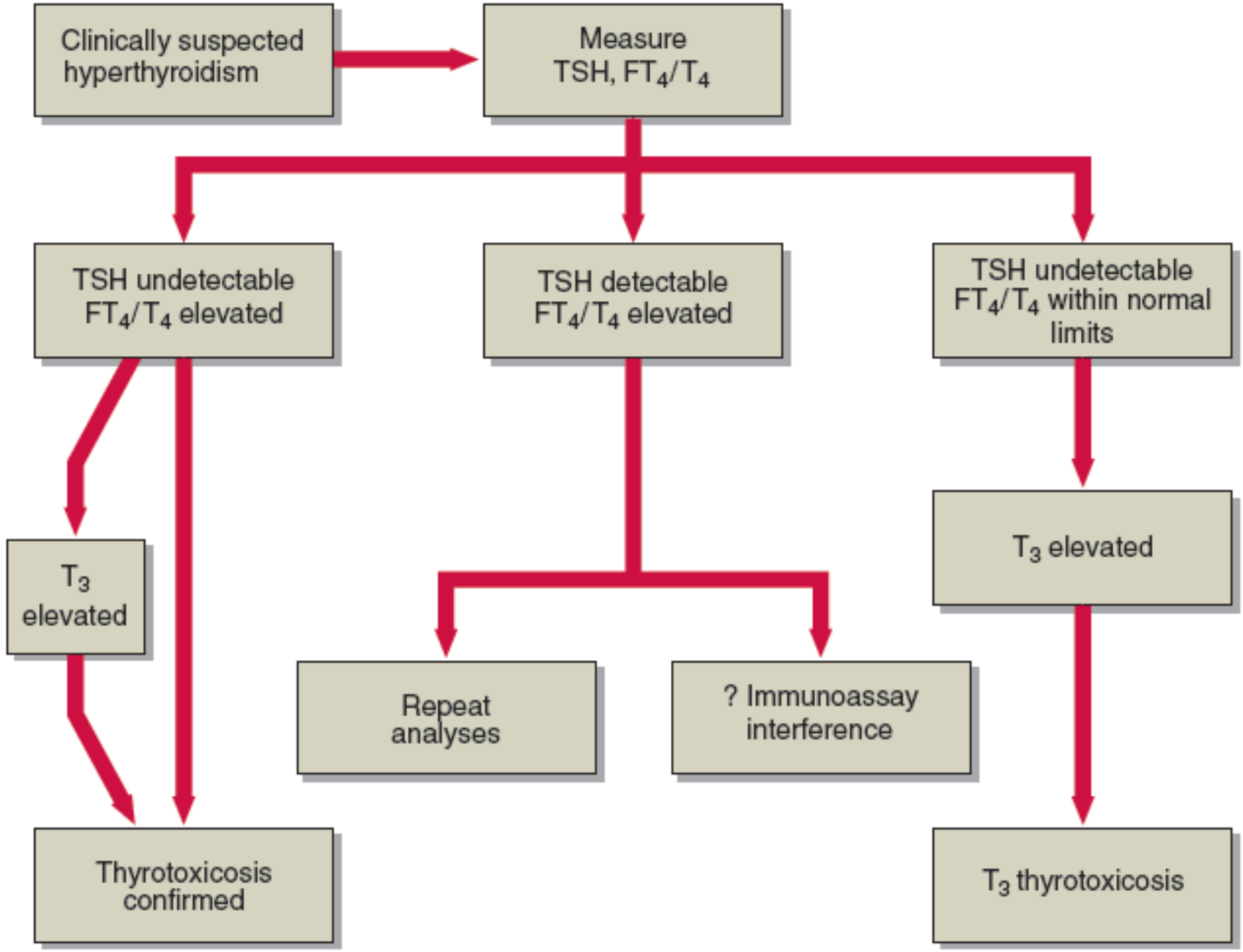


Fig 46.2 **Strategy for the biochemical investigation of suspected hyperthyroidism.**

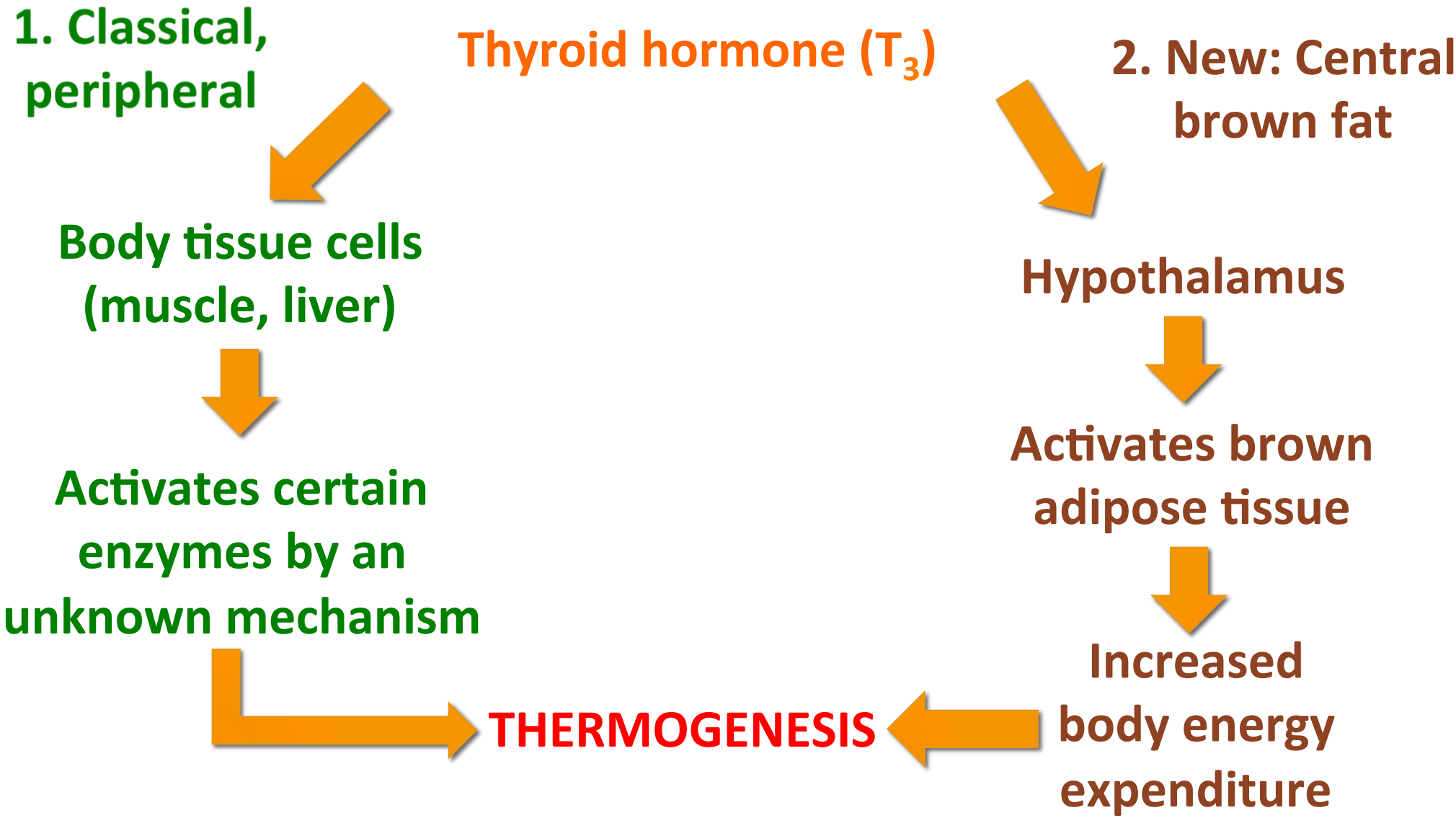
Thermogenesis (Heat production)

- Humans are **homeothermic** (keep constant body temp.)
- Tightly controlled **temperature homeostasis**
- Thermogenesis is of two types:
  - **Obligatory**: Heat production due to basal metabolic rate
  - **Facultative**: On-demand extra heat production from metabolic activity in brown adipose tissue, skeletal muscle, etc.
- Facultative thermogenesis in brown adipose tissue is stimulated by sympathetic nervous system

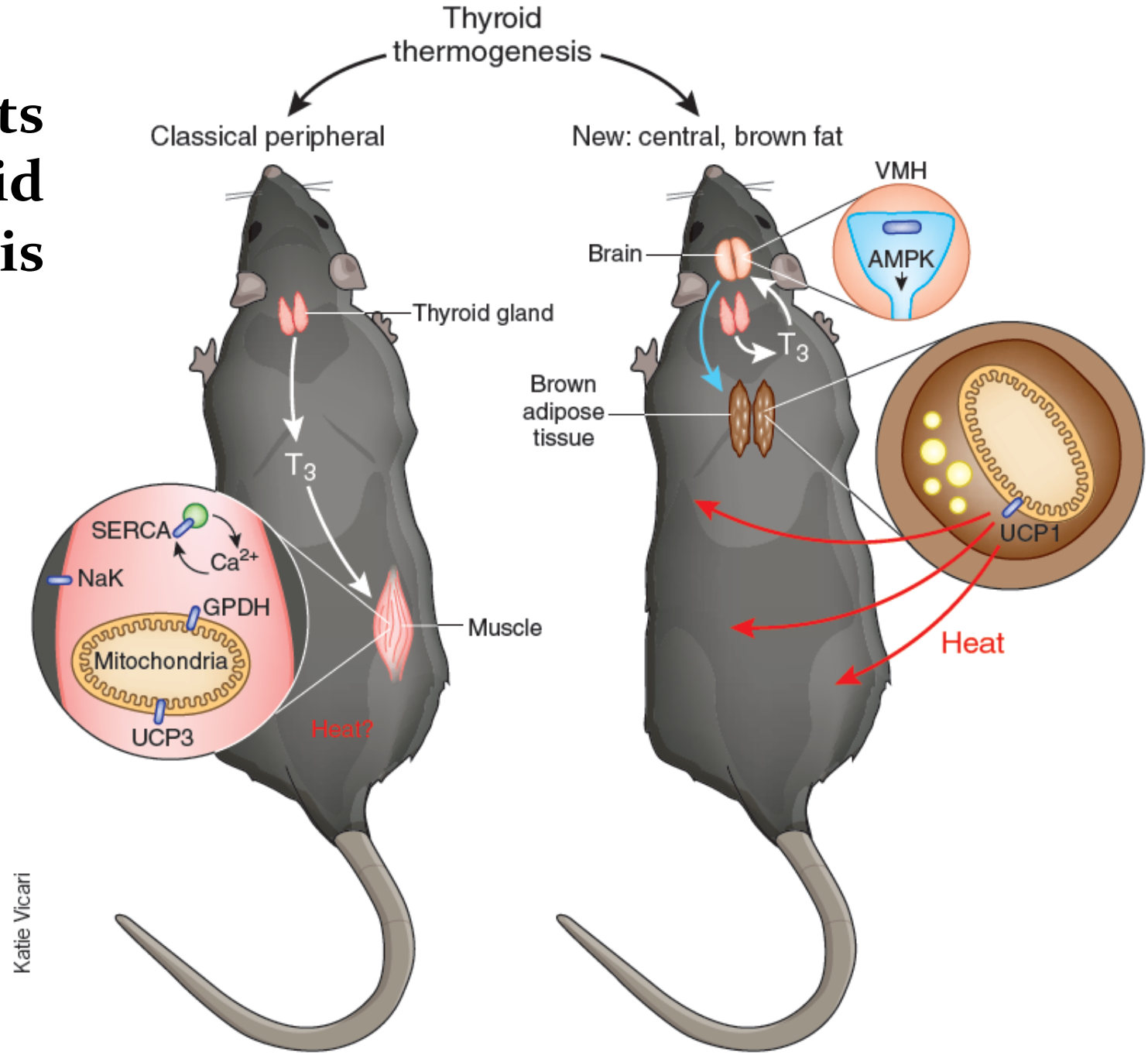
Thyroid Hormone and Thermogenesis

- Thyroid hormone plays essential roles in thermogenesis
- It upregulates body temperature set by the brain
- It acts centrally on the hypothalamus that controls brown adipose tissue for thermogenesis

Two concepts of thyroid thermogenesis



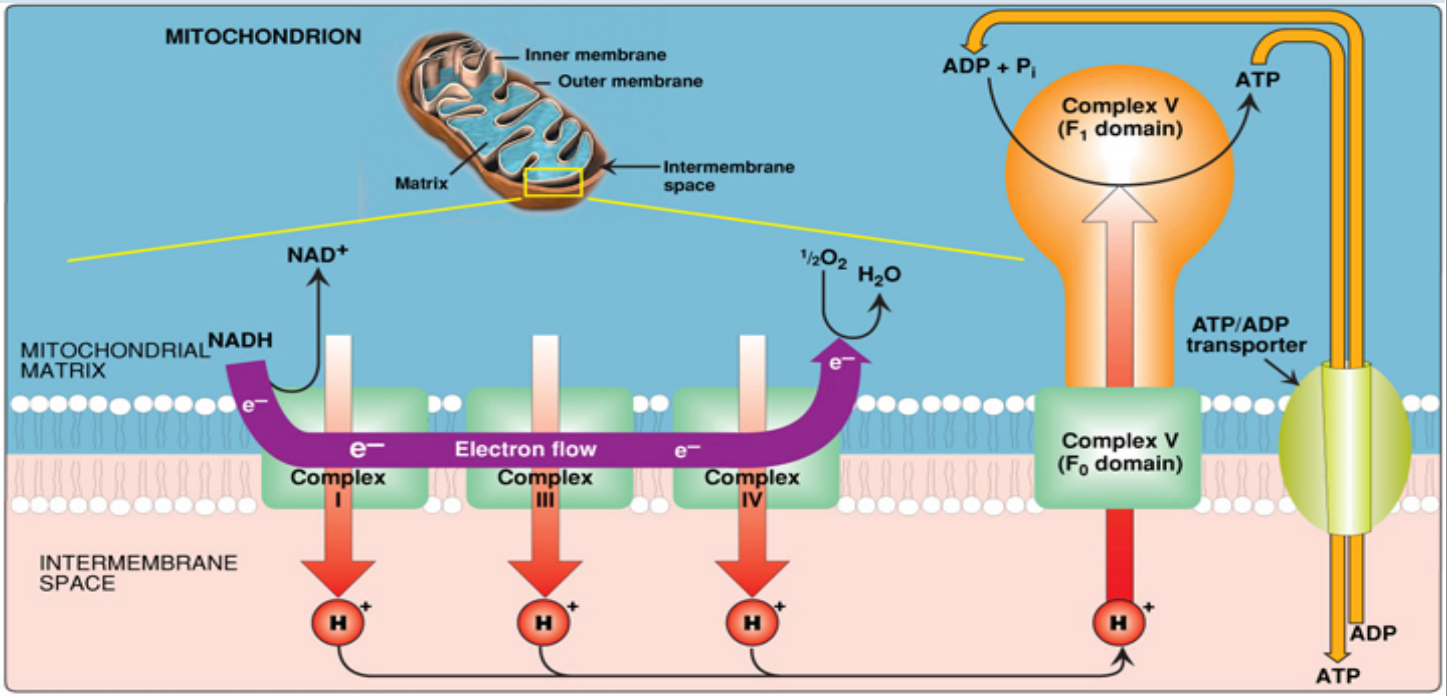
Two concepts of thyroid thermogenesis

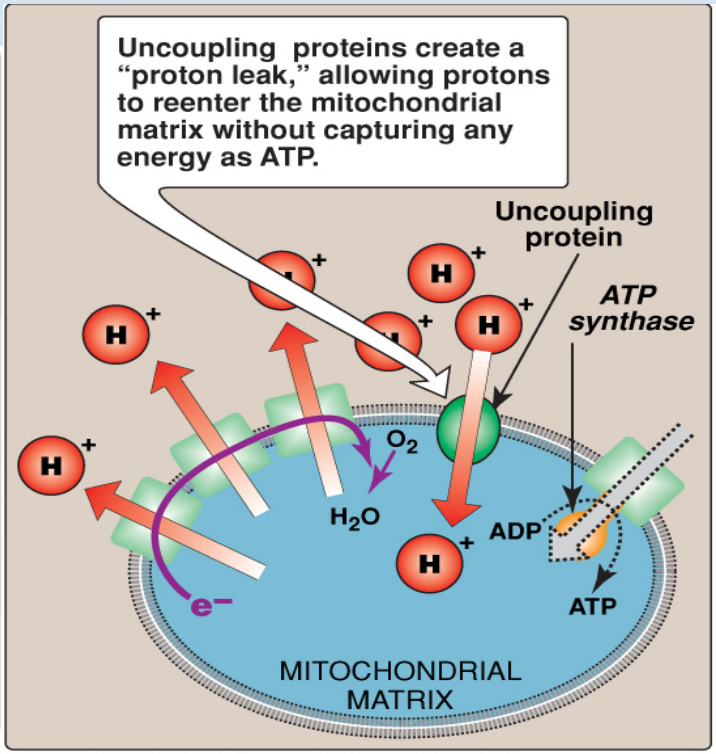


- In respiratory chain, some protons reenter the mitochondrial matrix thru uncoupling proteins (UCPs) without ATP synthesis
- These protons are released as heat
- Thyroid hormone regulates mitochondrial UCPs

Examples:

- UCP1 in brown adipose tissue
- UCP3 in muscle, other tissues





Take home message

- Thyroid hormones are synthesized in the thyroid gland by iodination, coupling and binding to thyroglobulin protein
- Thyroid hormones regulate metabolism and thermogenesis in the body
- It is regulated by hypothalamic-pituitary-thyroid axis
- Thyroid function tests such as TSH, total and free T_4 and T_3, and antibodies help diagnose and follow up thyroid disorders
- Goiter, hypo- and hyperthyroidism are due to abnormalities in thyroid functions

References

- Clinical Biochemistry: An Illustrated Colour Text, 5th Edition 2013, Allan Gaw, pp. 88-93, Churchill Livingstone, UK.

- Nedergaard, J and Cannon, B. Thyroid hormones: igniting brown fat via the brain. *Nature Medicine*, Volume 16, Number 9, pp. 965-967, 2010.